REMARKS

Applicants submit the following supplemental remarks and Declaration of Pramod K. Srivastava under 37 C.F.R. § 1.132 ("the Srivastava Declaration"), to supplement and support Applicants' response to the Examiner's rejection for lack of enablement.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR ENABLEMENT SHOULD BE WITHDRAWN

Claims 75, 97, 99-101, 104-112, 121-122, and 129-132 have been rejected under 35 U.S.C. § 112, first paragraph, with the Examiner contending that the claimed methods of treatment and prevention are not enabled because one skilled in the art would have to engage in undue experimentation as the specification has not taught how to accomplish treatment or prevention of autoimmune disorders. Applicants respectfully submit that the claims, as amended, are fully supported and enabled by the specification as described in detail below.

The Examiner's attention is invited to the Srivastava Declaration, which presents the results of experiments that extend the *in vitro* results disclosed in the specification with *in vivo* data that are predictive of the efficacy of the use of antagonists of HSP-CD91 interactions for treatment and prevention of autoimmune disorders.

As described therein, both alpha (2) macroglobulin and anti-CD91 antibodies effectively interfere with alpha (2) macroglobulin receptor and can successfully suppress an immune response *in vivo* (see ¶¶ 8-10 of the Srivastava Declaration and Figures 1 and 2 thereof, see Appendix 2). These results directly support the teachings of the specification by showing that antagonists of CD91-HSP interaction, such as an anti-CD91 antibody or alpha (2) macroglobulin, can be used to block antigen presentation in a mammal. In particular, the results presented in ¶¶ 8-10 of the Srivastava Declaration confirm and extend the *in vitro*

results disclosed in the specification which demonstrate that anti-CD91 antibodies inhibit the re-presentation of HSP-peptide (AH1) complexes (see specification at page 82, lines 28-37 of the specification).

The results presented in ¶¶ 8-10 of the Srivastava Declaration demonstrate *in vivo* that an antagonist of an HSP-CD91 interaction, such as anti-CD91 antibody or alpha (2) macroglobulin, blocked re-presentation of HSP-peptide complexes, and effectively suppressed an immune response *in vivo*. Thus, the compositions and methods taught in the specification, including an anti-CD91 antibody, can be used to effectively inhibit re-presentation of a peptide and suppress an immune response *in vivo*, in light of the disclosure in the specification that alpha (2) macroglobulin and anti-CD91 antibody have the same effect of inhibiting re-presentation of peptides [see specification at Figure 4, showing that alpha (2) macroglobulin inhibits re-presentation of gp96-chaperoned AH1 peptide by macrophage; Figure 9B, showing re-presentation of AH1-19 complexed to gp96, hsp90, hsp70, CRT or albumin carried out in the presence of increasing concentrations of alpha (2) macroglobulin indicate that the percent inhibition of re-presentation increases with the concentration of alpha (2) macroglobulin administered to RAW264.7 cells; and Figure 9C showing re-presentation of AH1-19 complexed to gp96, hsp90, hsp70, or calreticulin carried out in the presence of increasing concentrations of anti-CD91 antibody, indicating that the percent inhibition of re-presentation increases with the amount of anti-CD91 antibody administered to the RAW264.7 cells].

The Examiner's attention is further invited to ¶¶ 11 and 12 of the Srivastava Declaration, which present experimental results demonstrating the successful inhibition of an immune response in non-obese diabetic (NOD) mice, a mouse model of human autoimmune disorder. In the experiments described in ¶¶ 11 and 12 of the Srivastava Declaration, an antagonist of HSP-CD91 interaction, *i.e.*, alpha (2) macroglobulin, interfered with gp96-alpha

(2) macroglobulin receptor interactions and effectively delayed the onset of, *i.e.,* prevented, autoimmune diabetes in non-obese diabetic (NOD) mice, a commonly used animal model for an autoimmune disorder. These results support the teaching in the specification that animal models can be used to confirm *in vitro* results using antagonists of HSP-CD91 interactions to block antigen presentation and modulate immune responses (see specification, page 31, lines 10-16 and page 46, lines 19-22).

Thus, the experiments presented in the Srivastava Declaration demonstrate that one of skill in the art can readily follow the teachings of the specification, teaching the use of antagonists of HSP-CD91 interaction, *e.g.*, alpha (2) macroglobulin and anti-CD91 antibody, to block uptake of HSP-peptide complexes by the alpha (2) macroglobulin receptor activity, and thereby inhibit antigen re-presentation and suppress an immune response, without the need for undue experimentation (see specification, page 28, lines 7-11).

In conclusion, the *in vivo* results described in animal models presented in the Srivastava Declaration show that compounds that interfere with the uptake and re-presentation of a gp96-peptide complex by the alpha (2) macroglobulin receptor can be used to inhibit immune responses *in vivo*. These results corroborate the results of *in vitro* experiments described in the specification. Thus, the experiments presented in the Srivastava Declaration support the enablement of the claimed methods for the use of anti-CD91 antibodies to treat or prevent autoimmune disorders. In view of the results presented in the Srivastava Declaration submitted herewith, applicants assert that the claimed methods are enabled. Thus, the rejection has been obviated by the amendments to the claims and should be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application. It is estimated that no additional fee is necessary to file this amendment. In the event that an additional fee is required, please charge Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

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Enclosures